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Docket No. 46745 (48340) ES 3-11-03

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

APPLICANT:	J. Weidanz, et al.		
SERIAL NO.:	08/813,781	GROUP:	1644
FILED:	March 7, 1997	EXAMINER:	R. Schwadron

FOR: FUSION PROTEINS COMPRISING BACTERIOPHAGE COAT PROTEIN AND A SINGLE-CHAIN T CELL RECEPTOR

THE HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, D.C. 20231

APPELLANTS' BRIEF ON APPEAL
SUBMITTED PURSUANT TO 37 C.F.R. §1.192

In support of Appellants' appeal on October 17, 2002 of the Examiner's final rejection, mailed on June 17, 2002, submitted herewith is Appellants' Brief on Appeal.

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REAL PARTY IN INTEREST

The real party in interest is Sunol Molecular Corporation of Miramar, Florida. An assignment from the inventors to Dade International was recorded on August 18, 1997 at Reel/ Frame 8681/0081. An assignment from Dade International to Sunol Molecular Corporation is being filed on today's date under separate cover.

RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences known to Appellants or Appellants' representatives that will directly affect or be directly affected by or have a bearing on the Board's decision in the pending Appeal.

STATUS OF THE CLAIMS

Claims 1, 2, 4, 7, 8, 14, 67, 69, 71 and 72 stand finally rejected under 35 U.S.C. §103. All the claims are pending on appeal.

STATUS OF THE AMENDMENTS

Claims 1, 2, 4, 7, 8, 14, 67, 69, 71 and 72 on appeal are set forth in Exhibit A hereto. There has been no further amendment to the claims.

SUMMARY OF THE INVENTION

The claimed invention features a soluble fusion protein engineered to include a bacteriophage coat protein fused to a single-chain T cell receptor. The single-chain T cell receptor was itself designed to include an alpha-variable region ("V-α") fused to a beta-variable region ("V-β"). The single-chain T cell receptor forms a pocket that binds antigen when the antigen. The claimed soluble fusion protein further includes a beta-constant region ("C-β") region that can be fused to V-β, for example.

T cells help defend the body against infection. The cells have membrane bound receptors that bind foreign antigen with the assistance of a protein complex called "MHC". A key receptor is called the T cell receptor ("TCR"). The chemical structure and function of the TCR have been

extensively studied. For instance, it is known that formation of a TCR-antigen-MHC complex is an important step toward fighting infection.

The TCR as a heterodimer with one α chain and one β chain.[1] See **Exhibit A (i).** Each of these chains passes from the exterior of the T cell, through the cell membrane, and into the cell interior (cytosol). The α and β chains each include a variable (V-α, V-β) region that cooperate to form an antigen binding pocket. The regions are "variable" because its chemical structure can be changed to make a pocket that fits another antigen. Each of the V-α and V-β regions are associated with a constant (C) region.

TCR heterodimers have been difficult to isolate from T cells. This has hindered study of the receptor. One approach to address the problem has been to make single-chain T cell receptors ("scTCRs"). These synthetic receptors include, on one chain instead of two, a fused V-α and V-β region. See **Exhibit A (ii).** It has been customary to space the V-α and V-β regions from each other with a flexible linker to allow the regions to make an antigen binding pocket. Unfortunately, many scTCRs have still proven to be difficult to make and use.

Appellants discovered that by adding a bacteriophage coat protein to the scTCR, it is possible to produce a fully soluble and functional scTCR. In nature, the coat protein encapsulates bacterial viruses called "phages" or "bacteriophages". Unlike prior scTCRs, the claimed fusion proteins were found to be fully soluble, functional, and obtainable in significant quantities without difficulty. The claimed fusion proteins have a wide spectrum of important uses as described throughout the instant patent application.

None of the art of record in this case shows an attempt to make a scTCR that includes a fused bacteriophage coat protein.

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[1] A textbook in the field describes the TCR as "a heterodimer composed of an α and a β polypeptide chain, both of which are glycosylated." See Alberts, B et al. (1989) in *Molecular Biology of the Cell*, 2nd Ed. Garland Publishing, Inc. New York at pg. 1037. By convention, a "heterodimer" such as the TCR properly has two chains (dimer) both of which are different (hetero) from the other.

Appellants wish to emphasize that "TCR" means the **heterodimeric** T cell receptor. The TCR is a membrane bound (insoluble) receptor in which the α and β chains cooperate to bind antigen. Reference to a "scTCR" means a synthetic **single-chain** molecule that includes the V-α and V-β regions bound together usually through a flexible linker. However unlike the TCR, the scTCR binds antigen with only one chain. Thus, the TCR and scTCR are structurally distinct proteins that can bind the same antigen but do so differently. Compare **Exhibit A (i)-(ii).**

ISSUE

This appeal presents the issue of whether the Examiner erred in rejecting claims 1, 2, 4, 7, 8, 14, 67, 69, 71 and 72 under 35 U.S.C. § 103 in view of Chung, S. et al. (1994) *Proc. Natl. Acad. Sci. (USA)* 91: 12654 in view of U.S Pat. No. 5,759,817 to Barbas, Onda, T et al. (1996) *Mol. Immunol.* 32: 1387; and Huse et al. (1992) *J. Immunol.* 149: 3914. Appellants will refer to these citations as "Chung", "Barbas", "Onda" and "Huse", respectively; unless stated otherwise. There are no other pending rejections of record in this case.

GROUPING OF THE CLAIMS

All of claims 1, 2, 4, 7, 8, 14, 67, 71 and 72 stand or fall together for the purpose of the present appeal.

CASE HISTORY

In consideration of the Examiner's position in this case, Appellants have summarized the prosecution history with respect to the 35 U.S.C. §103 rejection at issue. A more detailed discussion of Appellants' rebuttal to those arguments will follow under Argument.

A. A patent application was filed on March 7, 1997 with 59 claims and assigned Serial No.: 08/813,781 by the USPTO.

B. An Office Action was mailed to Appellants on August 25, 2000 by Examiner Schwadron. The Examiner stated the following with respect to the §103 rejection on appeal:

> Claims 1, 2, 4, 7, 8, 14, 67, 69, 71, 72 are rejected under 35 U.S.C. 103(a) as unpatentable over Chung et al. in view of Barbas US 5,759,817 (filed Jan. 27,

1992), Onda et al. (Molecular Immunology 32:1387, 1995), and Huse et al. J. Immunology 149:3914. 1992

Chung et al. teaches a single chain T cell receptor which specifically binds to peptide ligand (see abstract). Chung et al. further teaches one embodiment of human single chain TCR in which C-terminus of V α domain is linked to N-terminus of V β chain via a 15 amino acid residue flexible amino acid liner and the C-terminus of the V β chain is linked to the beta chain constant domain (see Figure 1). In one embodiment the C terminus of V β chain is linked to a alkaline phosphatase (PI) protein tag (see page 12655). Chung et also teach that the purpose of the linker is to enhance the binding characteristics of the soluble T cell receptor and that linkers of about 10 to 30 amino acid residues would be considered to be sufficient. Chung et al. teach that the TCR fusion protein can bind antigenic protein, thus teaching that the TCR fusion protein comprises an antigen binding pocket. Chung et al. teaches a TCR fusion protein comprising V-α-peptide linker-V β-C β linked to GPI anchor and expression of such a fusion protein in a transfected eukaryotic cell (see results section). Chung et al. disclose that the soluble form of TCR protein could be readily obtained by enzymatic cleavage with phosphatidylinostol-specific phospholipase C (PI-PLC) (see page 12656). Chung et al. teaches expression of said TCR fusion protein in a bacterial cell system in which the N terminus of the Cβ region is linked to a histidine protein tag. Chung et al. also disclose a scTCR in which comprises V-α-peptide linker-V β-C β GPI in which the Cβ component consists of the β chain sequence ending right before the last cysteine (the sixth cysteine) (see page 12655). Chung et al. further teach that TCR fusion proteins which do not contain the CB do not fold into the native conformation. The scTCR disclosed by Chung et al. meet the length limitations of the Vα. and Vβ region recited in claims 69 and 71. Chung et al. teach a soluble fusion protein comprising a Vα-peptide linker-Vβ-Cβ fragment-protein tag (eg. GPI). **Chung et al. does not teach a TCR fusion protein further comprising bacteriophage VIII coat protein.**

However, Barbas discloses a soluble fusion protein comprising a bacteriophage coat protein fragment covalently linked to a single-chain heterodimeric receptor (see abstract and column 15, lines 27-28, in particular). Barbas also discloses that the fusion protein may comprise domains of heterodimeric proteins derived from several ligand binding proteins, including immunoglobulins and T cell receptors (see column 17, lines 62-66 and column 19, lines, 9-28. Barbas discloses that T cell receptor comprises alpha and beta chains each having a variable(V) and constant(C) region and T cell receptor has similarities in genetic organization and function to immunoglobulins (see column 19, lines 19-22, in particular). Barbas also teaches that bacteriophage coat protein may be derived from cpIII or cpVIII (see column 31, lines 10-28, in particular). Barbas discloses that expression vectors expressing soluble fusion proteins in which the ligand binding region is fused to bacteria coat protein allows the expression of the multiple fusion proteins on the surface of phage particles IE approximately 2700 cpVIII heterodimer receptor molecules per phage particle (see column 39 line 64 through column 40, line 7, in particular). Barbas further

discloses that a short length of amino acid sequence at the amino end of a protein (IE a protein tag) directs the protein to periplasmic space (see column 8, lines 49-55, in particular. One embodiment of the invention is disclosed to be a fusion protein comprising in sequence a leader sequence-peptide linker-V region amino acid residue-peptide linker-phage coat protein and that in one embodiment, the second linker can define a proteolytic cleavage site which allows the heterodimeric receptor to be cleaved from the bacteriophage coat protein to which it is attached (see column 14, lines 60-65). **Thus Barbas discloses but does not exemplify a soluble fusion protein comprising a bacteriophage coat protein covalently linked to T cell receptor domains.**[2]

Onda et al. disclose a soluble fusion protein comprising a bacteriophage coat protein covalently linked to a single-chain T cell receptor by a peptide linker sequence wherein the single TCR chain is the alpha chain and the bacteriophage coat protein is cpVIII (see abstract and Figure 1, in particular). Onda et al. also teach that TCR-bacteriophage coat protein fusion protein can be used to study specific binding interactions of the TCR chain to antigenic ligands (see paragraph bridging pages 1394-1395, in particular).

Huse et al. teach that fusion proteins comprising a single chain fusion protein comprising Fab fragment of immunoglobulin (which comprises the antigen binding pocket of the immunoglobulin molecule) and bacteriophage VIII coat protein can be produced and display the fusion protein when expressed in a M13 derived vector. Huse et al. further teach that bacteriophage VIII coat protein fusion protein can recovered from culture medium or from the periplasmic space (see abstract).

Therefore it would have been prima facie obvious to one with ordinary skill in the art at the time the invention was made to make a soluble TCR fusion protein comprising the Vα..-peptide linker-Vβ -Cb fragment-protein taught by Chung et al. linked to a bacteriophage VIII coat protein because **Barbas et al. and Onda et al. teach TCR-bacteriophage VIII coat fusion proteins can be used to study antigen binding properties of such a fusion protein** and Huse et al. teach that fusion proteins comprising bacteriophage VIII coat protein can be produced in bacteria and recovered in relatively large quantities.

One with skill in the art would be motivated to make such a fusion protein to study the antigen binding region of the TCR component or to use the protein to elicit anti-idiotypic antibodies. One with skill in the art would be motivated to make such a fusion protein in which the Vα and Vβ region was derived from

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[2] Examiner Schwadron withdrew this statement in the next Office Action dated June 17, 2002 (see below). The statement was originally made by a prior Examiner (Lubet) in a related §103 rejection that has been withdrawn. In that earlier rejection, Lubet argued that Barbas and Onda do not teach a soluble fusion protein in which a single-chain TCR linked to a bacteriophage coat protein. See the Office Action dated June 23, 1998 at pg. 8, part B. In the §103 rejection on appeal, Examiner Schwadron argued that Barbas and Onda teach use of TCR-bacteriophage VIII fusion protein. That molecule, a heterodimeric T cell receptor fusion protein, is not the claimed invention.

human TCR in order to study human TCR properties or to elicit anti-idiotypic antibodies to the TCR component of the protein.

The preceding grounds of rejection have been maintained since the August 25, 2000 Office Action despite Appellants' rebuttal argument and claim amendments discussed below.

C. On October 25, 2000, Appellants' representative met with Examiner Schwadron at the USPTO and discussed the art cited. No agreement was reached.

D. Appellants submitted a response to the rejection set forth in paragraph B, above, on February 22, 2001. In that response, Appellants rebutted the prima facie obviousness argument by pointing out: **1)** that the cited references did not teach or suggest that the membrane "anchor" of Chung's single-chain TCR (GPI: a membrane protein) could be substituted with the bacteriophage coat protein of Barbas' TCR; **2)** that there was no reasonable expectation that the substitution (switching Chung's anchor for Barbas' phage coat protein) could be achieved in view of substantial differences between scTCRs and TCRs; and **3)** that the Examiner's citation of Onda was not correct ie., it does not disclose TCR-bacteriophage coat protein fusions, but instead, dwelt on smaller constructs having only a V-α chain (but no V-β chain). Onda characterized his constructs as having "unusual" binding properties that were not characteristic of TCRs. A subset of such constructs were reported by Onda not to work at all.

Appellants also discussed the **Holler** reference: a peer-reviewed scientific article from the U.S. Academy of Sciences (*PNAS (USA)* (2000) 97: 5387 at 5389). Holler provided independent and objective evidence of the **long-felt need and failure of others** in the field to make and use the claimed fusion molecules. Specifically, Holler stated that phage display had not yet proven successful in the engineering of scTCRs.[3]

[3] By "phage display" is meant the process of making a recombinant bacteriophage expressing the scTCR as part of the phage protein coat. After infecting bacteria with a recombinant phage engineered to produce the scTCR, the protein would be "displayed" on the bacterial cell surface as bacteriophage. The scTCR "displayed" in this manner would be amendable to engineering.

E. In response to the Appellants' arguments in paragraph D above, the Examiner issued a Final Office Action dated June 17, 2002.[4] The Examiner maintained the prima facie rejection and stated:

> Regarding appellants comments, while **heterodimeric molecules are a preferred embodiment** disclosed in Barbas et al., Barbas et al. disclose: "In another embodiment, the present invention contemplates a polypeptide comprising an insert domain flanked by an amini-terminal secretion signal domain and a carboxy-terminal filamentous phage coat protein membrane anchor domain." (column 14, first complete paragraph).
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> Barbas et al. further disclose than said construct could include a **"receptor protein"** (column 14, second paragraph), indicating that the disclosed method could be used for receptors per se (eg. single chain or heterodimeric or single chain heteromers). Single chain T cell receptors were known in the art (see Chung et al.).
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> Regarding appellants comments about the single chain TCR taught by Chung et al.,
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> Chung et al. teach that the GPI anchor is cleaved and the soluble TCR still has all the antigen binding properties of the TCR (see pages 12656-12658). Thus, the GPI anchor is not required for the soluble TCR to function, it is just used in one particular method of making the soluble TCR. Regarding motivation to create the claimed invention, **Chung et al. discloses that it would be desirable to produce their TCR in a phage display system (see page 12658, first column).** In addition, Barbas et al. teach the advantages of their system for the production of peptides. Regarding reasonable expectation of success, both Barbas et al. and Chung et al. disclose use of phage display systems to produce single chain antibodies (see column 2, third paragraph from bottom and page 12658, first column). In addition, the soluble single chain TCR molecules functions with or without the GPI linker indicating that the construct itself is functional.
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> Regarding appellants comments about Holler et al., said publication was published in May 2000. In the amendment filed 6/3/2000, applicant submitted a publication by Weidanz et al. (J. Imm. Methods 1998) which discloses the claimed invention. Thus, **it appears that Holler et al. simply are not familiar with the prior art. Thus, the comments of Holler et al. carry no weight because two years prior to the Holler et al. publication, Weidanz et al. had already published data regarding the production of single chain TCR using**

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[4] The Examiner essentially repeated his rejection of the claims as set forth in the August 25, 2000 rejection. But see footnote 1. With respect to Examiner Schwadron's discussion about Holler, Appellants submitted Weidanz et al. as part of a Rule 132 Declaration to address an obviousness rejection that has since been withdrawn. The reference provided evidence that a particular scTCR-bacteriophage coat protein vector (pKC44) was capable of forming an antigen binding site when expressed. The reference is not prior art to the present application.

bacteriophage. Furthermore, Holler et al. discloses a yeast system for producing a single chain TCR and it appears that the main focus of Holler et al. is to promote their system.

Regarding appellants comments about Onda et al., the instant rejection indicates that "**Onda et al. disclose a soluble fusion protein comprising a bacteriophage coat protein covalently linked to a single-chain T cell receptor** by a peptide linker sequence wherein the single TCR chain is the alpha chain and the bacteriophage coat protein is cpVIII (see abstract and Figure 1, in particular)". The art recognizes that the alpha and beta chains of the TCR generally both are involved in antigen binding. The art also recognizes that soluble TCR which bind antigen would have a variety of uses.

F. Appellants filed a Notice of Appeal on October 17, 2002.

ARGUMENTS

I. Summary of the Cited Art

A. Chung reports functional three-domain single-chain T cell receptors consisting of a human Vα and Vβ region that recognizes a particular antigen (HLA-DR2b/myelin basic protein). Chung determined that it was important to fuse a Cβ region to the Vβ region. Such a three domain construct, when linked to a synthetic cell membrane anchor (glycosyl phosphatidyl-inositol (GPI) or CD3ζ fragment), was found to be expressed and functional. Chung disclosed that the cell membrane anchor could be cleaved from the single-chain receptors to obtain soluble protein. See the Abstract.

Chung opined that his single-chain design "may allow" construction of TCR phage libraries and that such libraries "may be" tools for studying TCRs. See pg. 12658. However, there is no specific disclosure in Chung about how such libraries could be made or, if made, whether his single-chain TCRs could tolerate fusion of the bacteriophage coat protein. Chung does not report or suggest that the GPI or CD3ζ membrane anchor could be substituted with a bacteriophage coat protein. Even if there was such a teaching, there is no disclosure in the reference about whether a recombinant bacteriophage could tolerate Chung's scTCR as part of the phage coat.

B. Barbas discloses heterodimeric receptor libraries that use phagmids. In the Abstract, phage are taught to encapsulate a genome encoding first and second polypeptides of a receptor such as an antibody; in which the first and second polypeptides are integrated into the coat

matrix of the phage. Barbas generally discloses that such phage may include a polypeptide with an "insert domain" that has a receptor domain flanked by a secretion signal domain and a phage coat protein membrane anchor domain. Col. 14, lines 10-14. Heterodimeric receptors are preferred. See Col. 3, lines 1-41; Col. 14, lines 15-29; and Col. 15, lines 28-32. According to Barbas, there was some uncertainty in the field about which portions of bacteriophage coat proteins were needed for phage assembly. Col. 2, lines 19-46.

Barbas does not teach how to make or use a scTCR with or without a fused bacteriophage coat protein.

C. Onda reports use of a phage display system to explore binding interactions between the V-α region and antigen. Onda did not disclose use of the system to study TCR or single-chain TCR interactions. In the Abstract, Onda provides at pg. 1387:

> We utilized an M13 phage display system, designed for multivalent receptor display, to explore specific binding interactions between various **TCR α chains** and specific antigen in the absence of MHC.

That is, Onda fused **only** the V-α region to bacteriophage coat protein. The constructs **do not** include a V-β region and are **not scTCR fusion proteins.** Onda's fusions are much smaller TCR "half-molecules" lacking the V-β region and antigen binding pocket of Appellants' scTCR.

Onda at pg. 1395, col. 1, cautioned that his constructs were **unusual** and not typical of standard TCR interactions:

> Our results extend these findings by demonstrating that the dominant interactions of certain **TCRα chains** for peptide antigens may be sufficiently high that they can be analysed independently. However, these interactions are **quite unusual** in that they do not require the expression of the second TCR subunit or normal MHC and coreceptor interactions. **These results may raise concern that this model does not reflect typical TCR-ligand interactions.**

Significantly, only some of Onda's Vα chain fusion proteins were reported to bind antigen when fused to bacteriophage coat protein. At pg. 1395, col. 2 he states that:

> ...**only a subset of TCR Vα have capacity for direct interactions with antigen strong enough to be detectable in this system**.

Onda does not teach or suggest fusing a scTCR (V-α and V-β) to a bacteriophage fusion protein.

D. Huse described a phage vector system for screening and producing antibody F(ab) fragments.[5] Huse's system was reportedly used to produce free F(ab) and F(ab) displayed on the surface of bacteriophage. According to Huse however, not all attempts to produce F(ab) were successful. In more than a few instances, the recombinant bacteriophage made to produce the fusions apparently would not tolerate certain amounts of antibody protein. In describing attempts to display certain antibody H and L chains with his phage vector system, Huse stated on pg. 3919, col. 2 that:

> Phage titers of [phage vector] infected cultures were found to **decrease** relative to the level of F(ab)-pVIII fusion protein incorporation (cite omitted). Taken together, these results suggest that a **functionally viable phage particle may be able to tolerate a limited number of incorporated F(ab)-pVIII fusion products and that the amount of F(ab) incorporated into the phage coat may adversely affect phage titers and overall F(ab) yield.**

Huse does not disclose fusing a bacteriophage coat protein to a scTCR or TCR.

II. Summary of the Examiner's Argument

Grounds for the present rejection under 35 U.S.C §103 were formulated in the Office Action dated August 25, 2000. See paragraph B, above. The basis for the rejection has not changed substantially in the face of Appellants' arguments and claim amendments.

According to Appellants' understanding of the Examiner's alleged prima facie case, the primary references, Chung and Barbas, are alleged to teach a scTCR linked to a bacteriophage fusion protein. Onda and Barbas are relied on to teach that TCR-bacteriophage fusion proteins can be used to study antigen binding. Huse is used to teach that fusion proteins with the coat protein can be made in bacteria. The foundation of the Examiner's position is that because Barbas, Onda, and Huse teach some bacteriophage coat protein fusions, then it would be obvious to make fusions with Chung's scTCRs. Although facially somewhat plausible, the rejection is flawed on both scientific and legal principles as discussed herein.

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[5] F(ab) is an abbreviation for an antigen binding fragment of an antibody (fragment antigen binding). F(ab) is a heterodimer consisting of two different chains ie., the antibody light and heavy chain. F(ab) is readily made by cleaving whole antibodies with specific proteolytic enzymes.

III. The Examiner Erred in Rejecting Claims 1, 2, 4, 7, 8, 14, 67, 69, 71 and 72 as Being Obvious

A. Requirements of the prima facie case and its maintenance.

The Examiner erred in maintaining the obviousness rejection in the face of claim amendments and the state of the art as submitted made in this case and its parent. The Federal Circuit has reiterated that an Examiner's prima facie case is but a procedural tool of patent examination, with the express purpose of allocating the burdens of going forward as between the Examiner and Applicant. See In re Deckler 977 F.2d at 1449, citations omitted):

> Specifically, when obviousness is at issue, the examiner has the burden of persuasion and therefore the initial burden of production. Satisfying the burden of persuasion, constitutes a so-called prima facie showing. Once that burden is met, the applicant has the burden of production to demonstrate that the examiner's preliminary determination is not correct. The examiner, and if later involved, the Board, retain the ultimate burden of persuasion on this issue.

Clearly, as demonstrated herein, adequate evidence of the unobviousness of the claimed invention was provided by Appellants to shift the burden of persuasion to the Examiner.

In view thereof, it is requested that the Board review the obviousness question based on the invention as claimed, and the cited references, including all relevant parts thereof.

B. Standard For Reviewing An Obviousness Rejection under 35 USC §103.

The Federal Circuit has reiterated the manner in which obviousness rejections are to be reviewed. Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, "a proper analysis under section 103 requires, inter alia, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success." In re Vaeck, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991), cited In re Dow Chemical Co., 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). As the Federal Circuit emphasized by succinctly summarizing: "Both the suggestion and the reasonable expectation of success must be founded in

the prior art, not the Applicants' disclosure." Id. See also In re Merck & Co., Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

More recently, the Federal Circuit has reviewed the case law regarding 35 U.S.C. §103. See In re Sang-Su Lee 277 F.3d 1388, 61 U.S.P.Q.2d 1430 (Fed. Cir. 2002).

Should the Board adopt the Examiner's prima facie case, Appellants submit that the claimed invention would not have been obvious in view of the legal standard summarized above.

C. No Prima Facie Case of Obviousness

As noted above, the foundation of the Examiner' argument rests on the belief that it would be obvious to fuse Chung's scTCR to the bacteriophage coat protein of Barbas because, allegedly, Barbas and Onda teach TCR-bacteriophage coat fusion proteins and Huse discloses that fusion protein with such a coat can be made in bacteria.

For the Examiner's prima facie case to stand, it is imperative that he establish that: 1) The cited references disclose or suggest fusing a bacteriophage coat protein to Chung's scTCR; 2) there is a settled role for the bacteriophage coat protein in making fusion proteins; and that 3) one could fuse Chung's scTCR to Barbas' coat protein with a reasonable expectation of success.

The Examiner's position is not supported by any of these points. Barbas, as relied on, does not teach or suggest a scTCR or even fusion of a scTCR to a bacteriophage coat protein. Onda and Huse, when read in their entirety, exemplify uncertainty in the field about using the bacteriophage coat protein to make certain fusion proteins. Even Barbas admitted that there was some doubt about how much one could change certain bacteriophage coat proteins without hindering phage assembly. Moreover, some of Onda's and Huse' molecules did not work well. Others did not work at all. On top of that uncertainty is heaped additional doubt about whether Chung's "anchor" fragments could be substituted with the bacteriophage coat protein of Barbas. There was also doubt about whether the bacteriophage would tolerate fusion of the scTCR to its coat.

i) *Barbas and Onda does not teach or suggest a single-chain TCR (scTCR)*

In the Office Action dated August 25, 2000, Examiner Schwadron took the position that Barbas discloses:

> soluble fusion protein comprising a bacteriophage coat protein fragment covalently linked to a **single-chain heterodimeric receptor** (see the abstract and column 15, lines 27-28, in particular). Barbas also discloses that the **fusion protein may comprise domains of heterodimeric proteins derived from several ligand binding proteins,** including immunoglobulins and T cell receptors (see column 17, lines 62-66 and column 19, lines, 9-28. Barbas discloses that T cell receptor comprises alpha and beta chains each having a variable(V) and constant(C) region and T cell receptor has similarities in genetic organization and function to immunoglobulins (see column 19, lines 19-22, in particular).
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> * * * *
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> Thus **Barbas discloses but does not exemplify a soluble fusion protein comprising a bacteriophage coat protein covalently linked to T cell receptor domains**

The heterodimeric receptor proteins pointed out by the Examiner are not scTCRs. Heterodimeric proteins, and particularly the TCR of Barbas, are understood in the field to consist of two different α and β chains. Brief at pg. 1. Unlike the TCR, the scTCR of Appellants' claimed invention is a single-chain molecule with a V-α chain fused to a V-β chain. The position that Barbas discloses a "single-chain heterodimeric" receptor simply makes no sense. How can a single-chain molecule be a "heterodimer" when that requires two (dimer) different (hetero) chains? Brief at pg. 1 and footnote 1. Barbas could not have had the single-chain constructs of Onda and Chung in mind. Those references were published well after the priority date of the Barbas patent. Thus, nowhere in the reference is there any disclosure about how to make or use a scTCR.

Faced with this rebuttal, the Examiner took the position in the Final Office that Barbas' disclosure of "polypeptides comprising an insert domain" and "receptor proteins" should be read to include Chung's scTCRs. Also included in that sweeping reading of Barbas are "single chain or heterodimeric or single chain heteromers". That position is without merit. Too much is read from Barbas. It does not provide for any scTCR molecules. If the Examiner's overly-broad view of the patent is allowed to stand and sweep in scTCRs, even though Chung's were published well after Barbas' priority date, it will preempt any attempt to obtain patent protection for scTCR-bacteriophage coat fusion proteins. A principle focus of Barbas was to provide **heterodimeric** receptors linked to a phage coat protein. See the Title of the patent, the Abstract and col. 3, lines

1-41, for instance. Such receptors are not the fusion proteins Appellants claim and there is no suggestion in Barbas to make or use them.

Even assuming, *arguendo*, that the Examiner is correct and that Barbas taught or suggested a scTCR (years before Chung or Onda were published), one reading Barbas in that way would be confused in light of the accepted understanding in the field that a heterodimer such as the TCR is a complex of two different polypeptide chains. Brief at pp. 1 – 2 and footnote 1.

As captioned above, Onda does not disclose a TCR or scTCR fusion to bacteriophage coat protein as alleged by the Examiner in the August 25, 2000 and June 17, 2002 Office Actions. Instead, Onda reports fusion of **TCR α chains** to bacteriophage coat protein. See **Exhibit A (ii)** showing the TCR α chain as part of a larger scTCR. These constructs are significantly smaller (and less likely to cause solubility problems when fused to coat proteins) than the scTCR fusions Appellants successfully made.

Moreover, the Examiner ignored Onda's clear hesitation about reading too much from TCR α chain constructs that include a fused bacteriophage coat protein. According to Onda, the interactions of the constructs were **unusual and not typical of TCR-ligand interactions**. See above and Onda at pg. 1395, col. 1.

Importantly, only some of Onda's TCR α chain constructs even worked to bind antigen. See above and pg. 1395 of Onda at col. 2, second full paragraph.

According to Onda then, some TCR α chain-bacteriophage coat protein fusions work and some do not. Those that do work were viewed as "unusual" and "not typical". In view of this caution, one working in this field would not be encouraged to fuse a bacteriophage coat protein to a scTCR. None of the other cited references shed any light on Onda's clear hesitation to extend there findings to other TCR molecules.

The Examiner thus erred in trying to formulate a prima facie case by not giving due weight to all relevant portions of Onda. Contrary to this practice, it is well established that the

Examiner must consider all relevant portions of cited references, including those portions which substantially weaken her position. In particular, the former CCPA stated in In re Mercier 515 F.2d 1161, 185 USPQ at 778:

> The relevant portions of a reference include not only those teachings which would suggest particular aspects of an invention to one having ordinary skill in the art, but also those teachings which would lead such a person away from the claimed invention.

See also Phillips Petroleum Co. v. U.S. Steel Corp., 673 F.Supp. 1278, 1315, 6 USPQ2d 1065, 1093 (D.Del. 1987), *aff'd*, 865 F.2d 1247, 9 USPQ2d 1461 (Fed. Cir. 1989).

The Board is thus urged to take Onda in its entirety and to consider all relevant portions of it including the passages quoted above. Read in this way, as it should, the reference would lead one in this field to doubt whether it would be feasible to fuse a bacteriophage coat protein to a scTCR to produce a soluble and functional fusion protein.

ii) *Huse reported difficulties producing some bacteriophage coat protein fusions*

The Huse reference, as quoted above, reported that not all F(ab)-pVIII (bacteriophage) coat proteins could be made at high titre. That is, Huse stated that the bacteriophage may not tolerate some amounts of F(ab) constructs, thereby decreasing phage titres and overall F(ab) yield. See above and Huse at pg. 3919, col. 2. When Huse is read in its entirety, as it should, the Examiner's statement that "Huse et al. teach that fusion proteins comprising bacteriophage VIII coat protein can be produced in bacteria" is an unsupported generalization. Huse clearly found that some amounts of heterodimeric F(ab) constructs harmed the bacteriophage that carried them. In view of this warning, a worker in the field would have good reason to doubt whether a bacteriophage could be fused to a scTCR or even a heterodimer such as a TCR without considerable experimentation.

The Examiner took the position in the Final Office Action that Barbas and Chung provide a reasonable expectation that one could make the claimed fusion proteins:

> Regarding **reasonable expectation of success**, both Barbas et al. and Chung et al. disclose use of phage display systems to produce single chain antibodies (see column 2, third paragraph from bottom and page 12658, first column).

However as clearly illustrated by Huse, not all phage display systems using antibodies work as expected. Some amounts of heterodimeric F(ab) antibodies cause problems. Thus the Examiner's position is not supported by the art of record in this case.

The Board is thus requested to take Huse in its entirety and to consider all relevant portions of it including the passage quoted above. In re Mercier 515 F.2d 1161, 185 USPQ at 778; and Phillips Petroleum Co. v. U.S. Steel Corp., 673 F.Supp. 1278, 1315, 6 USPQ2d 1065, 1093 (D.Del. 1987), *aff'd*, 865 F.2d 1247, 9 USPQ2d 1461 (Fed. Cir. 1989).

The substantial uncertainties raised by Onda and Huse have not been addressed by the Examiner. No objective scientific work has been made of record to resolve or explain them. Read in their entirety, as they should, Onda and Huse point out problems about making and using some bacteriophage coat protein fusions. Even if one skilled in this field were to read Onda and Huse selectively and disregard their warnings, there is still nothing in the art relied on to suggest that one could make or use a scTCR fusion to a bacteriophage coat protein. Even Barbas admitted that there was uncertainty about what coat protein parts could be manipulated for phage assembly.

In marked contrast, Appellants have demonstrated that it is possible to fuse a bacteriophage coat protein to the scTCR and obtain fully soluble and functional fusion protein. See Appellants' patent specification at Example 1 (showing construction of soluble scTCR fusion proteins); Examples 2-3 (production of special vectors to make the scTCR fusion proteins); Example s 4-5 (expression of Appellants' soluble scTCR fusions); Example 6 (purification of the soluble scTCR fusion proteins); Examples 7-11 and 16 (characterization of particular scTCR fusion proteins); and Example 15 (analysis of a bacteriophage library expressing Appellants' scTCR).

Accordingly, the §103 rejection fails both prongs of the Federal Circuit test for determining obviousness. See In re Vaeck, *supra*; and In re Dow Chemical Co., *supra*. It is submitted that the Board reverse the obviousness rejection in light of this test.

Whether or not the Examiner is taking the position that it would be **obvious to try** to make the claimed scTCR fusion proteins, both the Board and Federal Circuit have made it quite clear that this is not a burden that Appellants must bear. In particular, the Court in In re O'Farrell, 7 USPQ 2d 1673 (1988) held at page 1681:

> The admonition that "obvious to try" is not the standard under §103 has been directed mainly at two kinds of error. In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.

See also Ex parte Old, 229 USPQ 196, 200 (1985).

While the Court in In re O'Farrell went on to state that while obviousness does not require absolute predictability of success, what is required under §103 is a reasonable expectation of success.

Thus whether those in the field may have been tempted to fuse a bacteriophage coat protein to a scTCR, the field would have been cautioned from doing so in view of the warnings of Onda, Huse and to some extent even Barbas. The Barbas patent does not disclose or suggest any scTCR fusion to the coat protein. Chung does nothing to remedy these defects. In short, the field's unsuccessful experience with some amounts of antibody heterodimers (Huse) and some single-chain constructs (Onda), provides at worst no basis for believing that fusion of a bacteriophage coat protein to an scTCR will work and at best, a reason to doubt that such a fusion will result in a fully soluble and functional protein.

iii) *No teaching or suggestion that Chung's "anchor" fragment could be substituted with Barbas' bacteriophage coat protein*

Chung reported TCRs linked to a cell membrane anchor (glycosysl phosphatidylinositol (GPI) or murine CD3 ζ chain). The anchor apparently helps to express the single-chain TCRs.

The anchor molecules are entirely different from the coat proteins of Barbas both in terms of chemical structure and function. For example, Chung's anchors are hydrophobic cell membrane proteins while those of Barbas are relatively more hydrophilic bacteriophage coat components. Chung's anchor apparently plants the scTCR in the membrane while the coat envelops the phage.

The Examiner has pointed to no teaching or suggestion in the cited art that Chung's anchor molecules could be substituted with Barbas' bacteriophage coat proteins. The obviousness rejection falls far short of establishing any nexus between Chung's anchors, which are attached to his scTCRs, and the coat proteins reported by Barbas.

iv) *Objective Evidence of Non-obviousness*

In addition to the lack of a prima facie case of obviousness, the strong objective evidence of non-obviousness presented during prosecution of this case further compels allowance of the claims.

Evidence of such objective indicia of non-obviousness, the so-called "secondary considerations" must be considered in all obviousness determinations. Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 1538-1539 (1983):

> Indeed, evidence of secondary consideration may often be the most probative and cogent evidence in the record. It may often establish that an invention appearing to have been obvious in light of the prior art was not. It is to be considered as part of all the evidence, not just when the decision-maker remains in doubt after reviewing the art.

See also Graham v. John Deere, 383 U.S. 1, 148 USPQ 459 (1966).

This standard set forth by the Federal Circuit applies not only during litigation of issued patents, but to a determination of patentability during ex parte prosecution as well. In re Sernaker, 702 F.2d. 989 217 USPQ 1, 7 (Fed. Cir. 1983). However, in the instant case, the Examiner is not properly considered evidence of "long felt need and failure of others" in maintaining the present § 103 rejection.

Specifically, Appellants' provided the Holler reference as indicating that the field longed to make the claimed fusion proteins but could not. Holler reported that phage display had not yet proven successful in making scTCRs despite what he saw as extensive structural similarity between antibodies and TCR V regions. Appellants' invention addressed this need and succeeded by providing soluble fusion molecules with a bacteriophage coat protein linked to the scTCR. The Holler reference is highly probative of the difficulties the field had in making these molecules and should be given substantial weight by Examiner Schwadron. MPEP 716.01(b).

The Examiner completely dismissed the Holler reference on grounds that **"Holler et al. simply not familiar with the prior art".** See Part D, above. That is no basis for disregarding the Holler's statement that the field wanted but failed to produce the claimed invention. Appellants are under no burden to provide evidence of Holler's knowledge of the art in order to have the reference considered as objective indicia of non-obviousness. See Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 1538-1539 (1983); In re Sernaker, 702 F.2d. 989 217 USPQ 1, 7 (Fed. Cir. 1983); and MPEP 716.01(b).

Moreover, Examiner Schwadron's citation of Weidanz et al. to support his disregard of Holler is clearly improper. That reference is not prior art and cannot serve as a basis for ignoring Holler or substantiating the obviousness rejection on appeal.

It is requested that the Board consider Holler as objective evidence that workers in the field wanted, but could not make, the claimed invention.

CONCLUSIONS

For the Examiner's prima facie case to stand, he has the burden of showing that: 1) The cited references disclose or suggest fusing a bacteriophage coat protein to a scTCR; 2) there is a settled role for the bacteriophage coat protein in making fusion proteins; and that 3) one could fuse Chung's scTCR to Barbas' coat protein with a reasonable expectation of success. These points have not been made by the Examiner.

As discussed above, Barbas does not disclose scTCRs. Moreover, there was significant uncertainty in the field about whether it was possible to fuse a bacteriophage coat protein to a scTCR as exemplified by Huse and Onda. In view of the cited art and in consideration of the Examiner's position, it could be argued that one might be motivated to test fusing the bacteriophage coat protein to Chung's scTCR in the hope of producing a soluble and function protein. But this is not the legal standard required by our case law. It is without a doubt not obvious from the art of record to make the claimed invention of a scTCR fused to a bacteriophage coat protein.

Appellants submit that they have overcome the Examiner's obviousness rejection in the view of all the facts and argument of record in this case. Simply put, one of skill in this area would not be able to predict, with any reasonable expectation of success, how to make and use the claimed invention.

Importantly, Appellants have provided experimental evidence clearly showing that it is indeed possible to make and use scTCR-bacteriophage coat protein fusions. See Examples 1-11, 15 and 16 as discussed above.

In summary, Appellants submit that the instant invention is both novel and unobvious. The arguments set forth above establish that non-obviousness.

A check for $160.00, the required fee for filing a Brief on Appeal, is enclosed herewith [37 C.F.R. 1.17(c)]. Also enclosed is a Petition for Extension of Time for two (2) months along with the requisite Petition fee of $205.00.

This Appeal Brief is being submitted on February 19, 2003 which is the next business day after two day Federal holiday (Feb. 17 was Presidents' Day and the PTO was closed on Feb. 18 due to a weather emergency). Accordingly, submission of the Brief is timely and within the two-month extension period.

Respectfully submitted,

Date: February 19, 2003

By: _____

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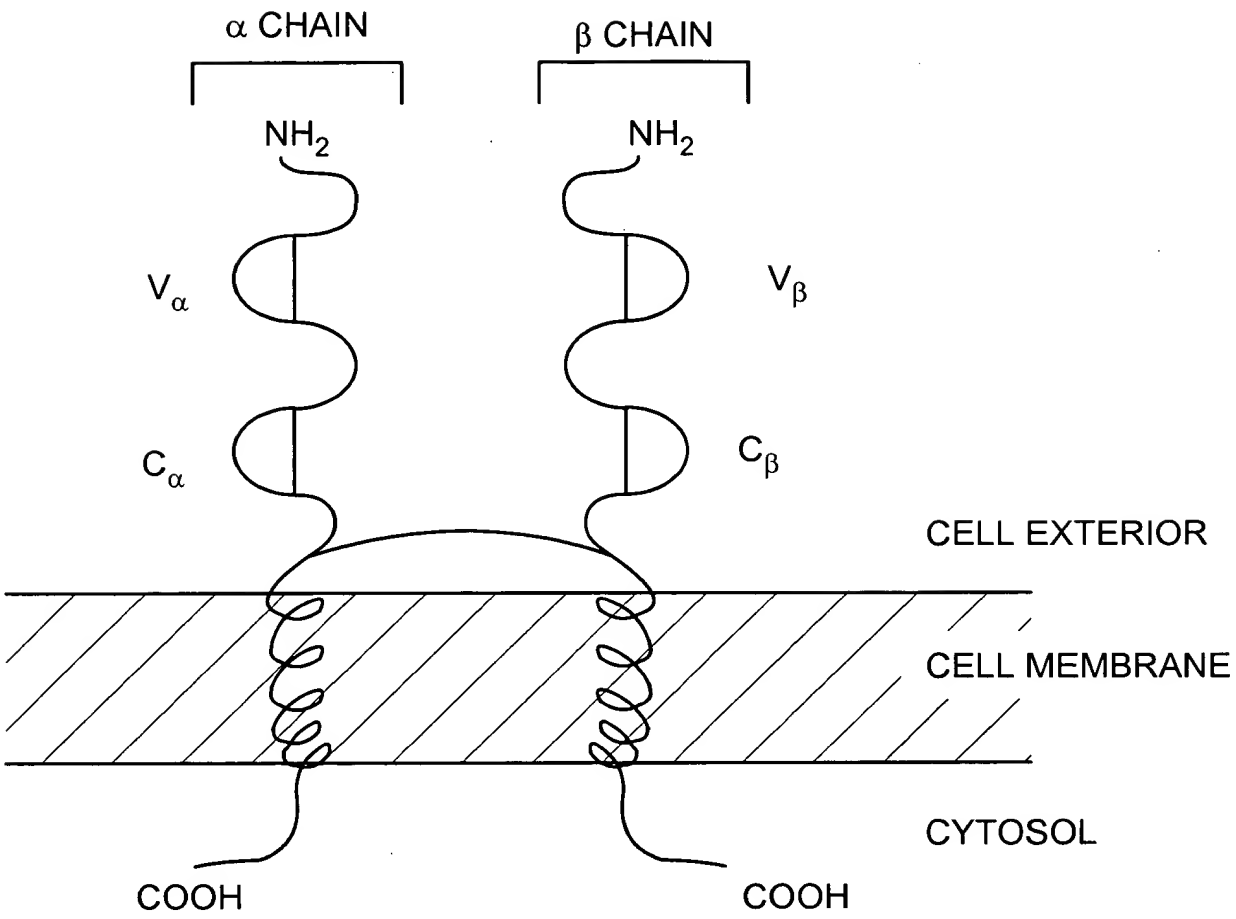
PATENT TRADEMARK OFFICE

EXHIBIT A



HETERODIMERIC TCR
(i)

SINGLE-CHAIN TCR
(ii)

EXHIBIT B
Claims 1, 2, 4, 7, 8, 14, 67, 69, 71 and 72
on appeal

What is claimed is:

1. A soluble fusion protein comprising a bacteriophage coat protein covalently linked to a single-chain T cell receptor comprising an antigen binding pocket, wherein the single-chain T cell receptor comprises a V-α region covalently linked to a V-β region by a peptide linker sequence that effectively positions the V-α region and the V-β region to form the antigen binding pocket, the soluble fusion protein further comprising a C-β region fragment.

2. The soluble fusion protein of claim 1, wherein the C-terminus of the V-α region is covalently linked by the peptide linker sequence to the N-terminus of V-β region.

4. The soluble fusion protein of claim 2 wherein the C-β region fragment is covalently linked between the C-terminus of the V-β region and the N-terminus of the bacteriophage coat protein.

7. The soluble fusion protein of claim 2, wherein the peptide linker sequence contains from approximately 2 to 20 amino acids.

8. The soluble fusion protein of claim 1, wherein the bacteriophage coat protein is gene III or gene VIII protein.

14. A soluble fusion protein comprising covalently linked in sequence: 1) a V-α region, 2) a peptide linker sequence, 3) a V-β region covalently linked to a C-β region fragment, and 4) a bacteriophage gene VIII protein, wherein the peptide linker sequence effectively positions the V-α region and the V-β region to form an antigen binding pocket.

67. The soluble fusion protein of claim 1, wherein the C-terminus of the V-β region is covalently linked to the N-terminus of a C-β region fragment.

69. The soluble fusion protein of claim 1, wherein the V-α region and the V-β region are about 200 to 400 amino acids in length.

71. The soluble fusion protein of claim 1, wherein the C-β region fragment is about 50 to 126 amino acids in length.

72. The soluble fusion protein of claim 70, wherein the C-β region fragment does not include a cysteine residue corresponding to position 127 of a full-length C-β region.

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